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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/587,189

04/03/2007

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EXAMINER

RODRIGUEZ-GARCIA, VALERIE

ART UNIT

PAPER NUMBER

4161

MAIL DATE

DELIVERY MODE

07/25/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/587,189	<b>Applicant(s)</b> ZINSER ET AL.	
	<b>Examiner</b> VALERIE RODRIGUEZ-GARCIA	<b>Art Unit</b> 4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. ____.                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>07/25/06, 08/28/06</u> .                                      | 6) <input type="checkbox"/> Other: ____.                          |

## DETAILED ACTION

### *Status of the Claims*

Claims 1-13 are currently pending and are the subject of this Office Action. This is the first Office Action on the merits of the claims.

### *Priority*

This application is a 371 of PCT/CH04/00063 filed on 02/05/2004. The earliest effective U.S. filing date has been determined to be 02/05/2004, the filing date of the application PCT/CH04/00063.

### *Objections*

### *Specification*

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The **abstract** should be in narrative form and **generally limited to a single paragraph** on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

In the instant case the **abstract is three paragraphs**.

### ***Claim Objections***

1. Claims 1-13 are objected to because of the following informalities: Independent claims 1 and 10 should start with the article, --A--, and dependent claims 2-9, 11-13 should start with --The--. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112 (1<sup>st</sup> paragraph)***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 8, 9 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process where the activation of the dibenzyl phosphite with elemental bromine or N-bromosuccinimide and the reaction of the activation product with 3-hydroxymethyl-5,5-diphenylimidazoline-2,4-dione are carried out in one operation and hydrogenation of the phosphoric acid 2,5-dioxo-4,4-diphenyl-imidazolidin-1-ylmethyl dibenzyl ester and the conversion of the 5,5-diphenyl-3-[phosphonooxy)methyl]imidazolidine-2,4-dione to its disodium salt is carried out in two steps or two operations, does not reasonably provide enablement for a process where the hydrogenation of the phosphoric acid 2,5-dioxo-4,4-diphenyl-imidazolidin-1-ylmethyl dibenzyl ester and the conversion of the 5,5-diphenyl-3-[phosphonooxy)methyl]imidazolidine-2,4-dione to its disodium salt is carried out in one operation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, no guidance is provided for a person skilled in the art to practice the process of hydrogenation of the phosphoric acid 2,5-

Art Unit: 1638

dioxo-4,4-diphenyl-imidazolidin-1-ylmethyl dibenzyl ester and conversion of the 5,5-diphenyl-3-[phosphonooxy)methyl]imidazolidine-2,4-dione to its disodium salt in “one operation” as claimed.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims recite a process of hydrogenation of the phosphoric acid 2,5-dioxo-4,4-diphenyl-imidazolidin-1-ylmethyl dibenzyl ester and conversion of the 5,5-diphenyl-3-[phosphonooxy)methyl]imidazolidine-2,4-dione to its disodium salt in one operation or step.

State of the prior art: Prior art describes two steps process for the hydrogenation and conversion to the disodium salt of the phosphoric acid 2,5-dioxo-4,4-diphenyl-imidazolidin-1-ylmethyl dibenzyl ester (US 6,022,975; U.S. 2005/0272706A1). Examples are lacking in the prior art of a one step or one operation method for the hydrogenation of the phosphoric acid 2,5-dioxo-4,4-diphenyl-imidazolidin-1-ylmethyl dibenzyl ester and conversion of the 5,5-diphenyl-3-[phosphonooxy)methyl]imidazolidine-2,4-dione to its disodium salt.

Existence of working examples/specification: The specification only discloses a two step or two operation process (p. 6 Example 2). There are no examples of the claimed one step process in the specification.

Art Unit: 1638

Amount of experimentation necessary: In order to practice the claimed method of hydrogenation and conversion to the disodium salt of the phosphoric acid 2,5-dioxo-4,4-diphenyl-imidazolidin-1-ylmethyl dibenzyl ester in one operation, one of ordinary skill in the art would have to investigate the reaction to be done, the reagents to be used which need to be compatible with all other reagents and the conditions to be used in the claimed one operation reaction. In other words, since there is no guidance or examples on how to do the claimed one operation reaction, one of ordinary skill would have to do all investigations from scratch.

It would require undue experimentation for one of ordinary skill in the art to practice the claimed invention in the full broad scope recited in the claims. Therefore, the claimed invention of a process of hydrogenation of the phosphoric acid 2,5-dioxo-4,4-diphenyl-imidazolidin-1-ylmethyl dibenzyl ester and conversion of the 5,5-diphenyl-3-[phosphonooxy)methyl]imidazolidine-2,4-dione to its disodium salt in one operation or step is not fully enabled by the instant specification.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claim 10 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Davis *et al.* (US 6,022,975; WO document cited in the IDS and ISR).

Davis *et al.* prepared disodium fosphenytoin (5,5-diphenyl-3-[(phosphonooxy)methyl]imidazolidine-2,4-dione disodium salt) by converting the phosphoric acid dibenzyl ester 2,5-dioxo-4,4-diphenyl-imidazolidin-1-ylmethyl ester, in a

single operation of catalytic hydrogenation, to (5,5-diphenyl-3-[(phosphonooxy)methyl]imidazolidine-2,4-dione and this was converted to its disodium salt (col. 5, Example 5).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

1. Claims 1-7 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis *et al.* (US 6,022,975; WO document cited in the IDS and ISR) in view of Oza *et al.* (J. Org. Chem. 1995; 60(12):3680-3684), further in view of Stowell *et al.* (Tetrahedron Lett. 1995; 36(11):1825-1826), Silverberg *et al.* (Tetrahedron Lett. 1996; 37(6): 771-774) and of Johnstone *et al.* (Chem. Rev. 1985; 85:129-170) and as evidenced by Kirsch *et al.* (US 2005/0272706A1).

The instant claims recite a process for the preparation of 5,5-diphenyl-3-[(phosphonooxy)methyl]imidazolidine-2,4-dione disodium salt or fosphenytoin.

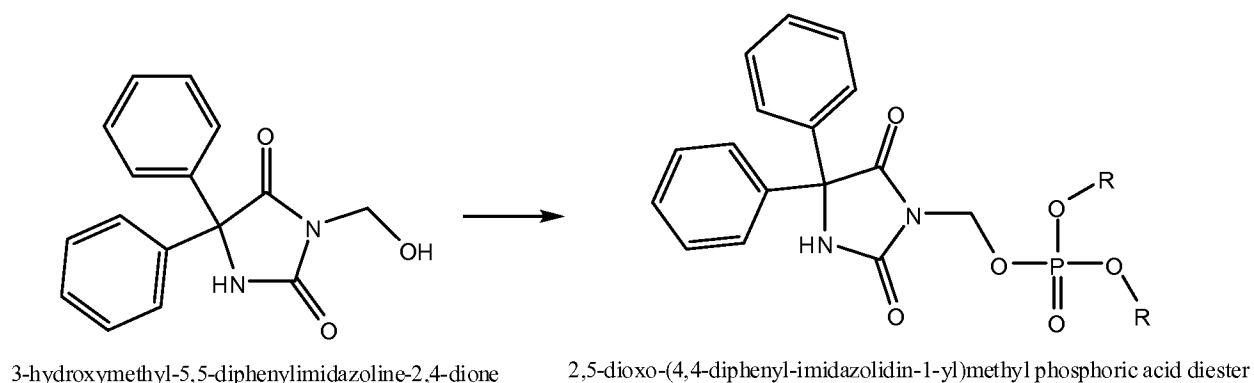
Fosphenytoin is a well known water-soluble prodrug of phenytoin used as anticonvulsant. Several syntheses have been disclosed and they all convert the hydroxyl group of hydroxymethylphenytoin to a good leaving group such as Cl, Br, or MsO and react it with a phosphonate salt.

Davis *et al.* disclose the synthesis of disodium fosphenytoin (5,5-diphenyl-3-[(phosphonooxy)methyl]imidazolidine-2,4-dione disodium salt) by converting 3-(hydroxymethyl)-5,5-diphenylimidazolidine-2,4-dione (in the figure below) to 3-chloromethylphenytoin or 3-bromomethylphenytoin, reacting this with an alkali metal phosphonate such as potassium or sodium dibenzylphosphonate, cleaving the two benzyl groups in the resulting diester by catalytic hydrogenation in the presence of palladium on carbon and, finally, converting it to the desired disodium salt by the addition of sodium hydroxide (col. 4-6, Examples 1-5). However, as evidenced by Kirsch *et al.*, Davis *et al.* process requires four steps to obtain the product and the reaction of 3-chloromethylphenytoin with the alkali metal phosphonates has an unsatisfactory behavior, which requires addition of catalytic amounts of potassium iodide in order to accelerate the reaction. This increases the cost of the reaction and introduces additional foreign salt into the mixture (p. 2, [0014]). Davis *et al.* do not teach the reaction of 3-(hydroxymethyl)-5,5-diphenylimidazolidine-2,4-dione with a phosphorous acid ester, such as dibenzyl phosphite, activated by an oxidizing agent, neither that the oxidizing agent is a halogenating agent, such as elemental bromine, nor that the activation of the phosphite and the reaction of its product with 3-(hydroxymethyl)-5,5-diphenylimidazolidine-2,4-dione are carried out in one step (claims 8, 9 and 13).

Methodology optimization for the process of producing the commercially available anticonvulsant disodium fosphenytoin is wanted. As shown by the processes currently known in the literature, the challenging step in the synthesis of disodium



fosphenytoin is the making of the 2,5-dioxo-4,4-diphenylimidazolidin-1-ylmethyl phosphoric acid diester (shown below).



Oza *et al.* teach the oxidative phosphorylation of alcohols with trimethyl phosphite/carbon tetrabromide in pyridine to provide the corresponding dimethyl phosphate esters (phosphoric acid diesters) in high yields. Oza *et al.* disclose that the reaction conditions are extremely mild and the reagents required are of very low cost, making this a useful method for the preparation of a wide variety of alkyl and aryl dimethyl phosphate esters (p. 3683, conclusion). In a very similar approach, Stowel *et al.* teach the oxidative phosphorylation of alcohols via the activation of trialkylphosphites with molecular iodine under very mild conditions to afford phosphate esters in quantitative yields (p. 1836, 1<sup>st</sup> paragraph). Silverberg *et al.* disclose the phosphorylation of phenols by converting dibenzyl phosphite to the reactive dibenzyl chlorophosphate by an *in situ* chlorination with carbon tetrachloride in acetonitrile.

As shown, there are several methods that claim to be simple, rapid and effective in the phosphorylation of alcohols. As such, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to make 3-

Art Unit: 1638

(hydroxymethyl)-5,5-diphenylimidazolidine-2,4-dione (as of the figure above) as disclosed by Davis *et al.* and to perform an oxidative phosphorylation by the reaction with trimethyl phosphite/carbon tetrabromide in pyridine, as disclosed by Oza *et al.* or by the reaction with a trialkyl phosphite/ I<sub>2</sub> in pyridine, as taught by Stowell *et al.*, or by the reaction of dibenzyl phosphite with carbon tetrachloride in acetonitrile, as disclosed by Silverberg *et al.*, to achieve the desired 2,5-dioxo-4,4-diphenylimidazolidin-1-ylmethyl phosphoric acid diester (as of the figure above). After obtaining the phosphoric acid diester, it is converted to the fosphenytoin final product by cleaving the ester groups by the same method of catalytic hydrogenation in the presence of palladium on carbon described by Davis *et al.* and converting it to the desired disodium salt by the addition of sodium hydroxide, also described by Davis *et al.*.

The phosphite used by Oza *et al.* is trimethyl phosphite, while Stowell *et al.* also investigates triethyl phosphite and tribenzyl phosphite all of instant claim 5. The oxidizing/halogenating agent used by Oza *et al.* is carbon tetrabromide of instant claims 2-3. Stowell *et al.* utilize elemental iodine. Silverberg *et al.* use dibenzyl phosphite (as in claims 6-9 and 13) activated with carbon tetrachloride. As shown by the cited references, the different oxidizing/halogenating agents disclosed are equivalent, they perform the same function. As such, if carbon tetrabromide, carbon tetrachloride or elemental iodine is used, it is obvious that other related oxidizing/halogenating agent such as elemental chlorine or elemental bromine can be utilized for activation of the phosphites.

### **Conclusion**

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to VALERIE RODRIGUEZ-GARCIA whose telephone number is (571)270-5865. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

VRG

/Ashwin Mehta/  
Primary Examiner, Technology Center 1600